Nerve Fiber Layer Defects with Normal Visual Fields

Do Normal Optic Disc and Normal Visual Field Indicate Absence of Glaucomatous Abnormality?

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Purpose: When the optic disc has normal appearance with no abnormalities in routine automated perimetry, the subject is not considered to have glaucoma. The purpose of this study is to show how such patients may have localized retinal nerve fiber layer defects with corresponding functional abnormality.

Methods: The authors selected eight eyes of eight patients who had a localized retinal nerve fiber layer defect extending within a few degrees from fovea but in whom the optic disc appearance and Humphrey 30-2 visual fields were normal. Of the eight patients, three had positive family history of glaucoma, two had suspected retinal nerve fiber layer abnormality in routine eye examination, two had increased intraocular pressure (IOP), and one had advanced low-tension glaucoma in one eye with a normal fellow eye. The authors examined the central 10° visual field with 1° resolution using Humphrey perimeter and the Ring and Centring programs of the high-pass resolution perimeter.

Results: A central field defect corresponding to retinal nerve fiber layer defect was found in six of eight patients: in both 10° Humphrey field and Centring programs (2 eyes), in Humphrey only (2 eyes), and in Centring only (2 eyes).

Conclusion: The results indicate that retinal nerve fiber layer photographs are helpful in diagnosing glaucoma because early glaucomatous abnormalities cannot be excluded without nerve fiber layer photography. Currently available routine perimetric examination programs do not always detect very early functional damage.

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The significance of retinal nerve fiber layer evaluation in the early diagnosis of glaucoma was first reported by Hoyt and Newman[1] over 20 years ago. Subsequent investigators showed that retinal nerve fiber layer defects may precede the onset of glaucomatous field loss by up to 6 years,[2–4] represent the first observable glaucoma damage after an optic disc hemorrhage[5,6] and be useful in screening for glaucoma.[7]

It is somewhat unexpected that retinal nerve fiber layer photography has not gained wider acceptance in general ophthalmic practice. In most clinical research protocols, the presence of visual field damage is prerequisite for the diagnosis of glaucoma. Patients with normal visual fields

and elevated intraocular pressure (IOP) are called ocular hypertensives despite the fact that they may have shown progressive structural changes years before measurable functional damage. Retinal nerve fiber layer defects and their progression are rarely taken into consideration.

Some patients, particularly those with small optic discs, may show retinal nerve fiber layer abnormalities despite normal optic disc appearance and normal routine automated threshold perimetry.[7,8] In such cases, profile perimetry performed with 1° resolution in several meridians may show a visual field defect.[6]

In this study, instead of using time-consuming profile perimetry, we wanted to examine the central 10° visual field more accurately using light sense perimetry with 1° resolution as well as high-pass resolution perimetry[9] in patients with a normal 30° field and a localized nerve fiber layer defect.

Patients and Methods

Patients

We selected eight patients who had a localized retinal nerve fiber layer defect in one eye (4 right and 4 left eyes) but normal appearance of the optic disc and normal automated visual field. The mean age (± standard deviation) of the four females and four males was 62 ± 10 years (range, 46–78 years).

Three patients had an eye examination because of positive family history of glaucoma. In two patients, retinal nerve fiber layer abnormality was suspected in routine eye examination. Two patients had been followed for increased IOP (>22 mmHg). One patient had advanced low-tension glaucoma in one eye; the fellow eye had normal IOP with no development of glaucomatous abnormalities in automated visual fields or optic disc during 5 years of follow-up before entering the study.

In all eyes, the wedge-shaped localized retinal nerve fiber layer defect extended within a few degrees from the fovea. The visual acuities were 1.1 or better with no clinically detectable macular degeneration. Three patients had a follow-up of 4, 5, and 7 years.

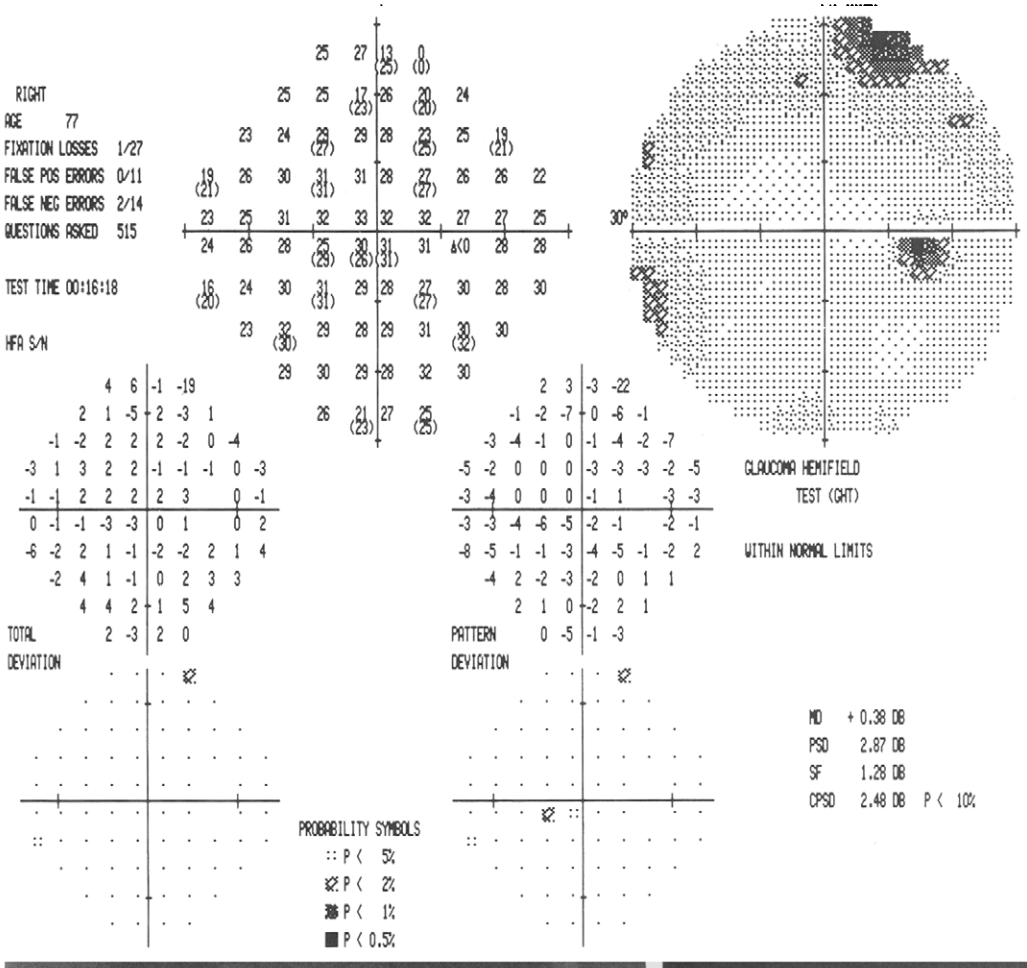
Methods

The 30° visual fields were examined with the Humphrey perimeter using program 30–2. The normality of visual fields was judged using the Glaucoma Hemifield Test of the Statpac 2 program.[10] In addition, no field fulfilled the criteria of a localized visual field defect in the protocol of the Low Tension Glaucoma Collaborative Study Group[11]: (1) at least three points in a cluster depressed 5 decibels or more from the age-corrected normal value, and (2) at least one of these points deviates more than 10 decibels from the normal value. The visual fields had to be reliable and at least three field examinations had been performed in all patients before entering the study.

The central 10° visual field was examined with 1° resolution using first the off-axis Humphrey 10-2 program and then a user-defined on-axis 8° field, both with 2° resolution. Because it is known that fluctuation depends both on the distance of the test point from fixation and the threshold value,[12] we defined lower threshold deviations to be significant in the 10° area. After pointwise comparison of the threshold values between the upper and lower hemifields, a localized visual field defect was defined to be present if the threshold of at least four points in a cluster deviated 4 decibels or more from the corresponding point in the opposite hemifield and this area corresponded in location to the retinal nerve fiber layer defect.

Table 1. Results of Examination of the Visual Fields of Eight Patients with a Retinal Nerve Fiber Layer Defect and Normal Optic Disc Appearance and Normal Humphrey 30-2 Visual Field

Case No.	Retinal Nerve Fiber Layer Defect	Humphrey 10-2 and Central 8°	Ring (30°)	Centring (8°)
1		Absolute, inferior defect 4°–8° from fixation	Inferior nasal step and paracentral scotoma	Deep inferior defect below fixation
2		No defect	No defect	No defect
3		Relative superior defect 5°–7° from fixation	No defect	No defect
4		No defect	No defect	No defect
5		Relative inferior defect 5°–7° from fixation	No defect	No defect
6		No defect	No defect	Deep inferior defect below fixation
7		No defect	No defect	Defect below fixation
8		Relative superior defect 6°–10° from fixation	Shallow arcuate scotoma	Paracentral depression



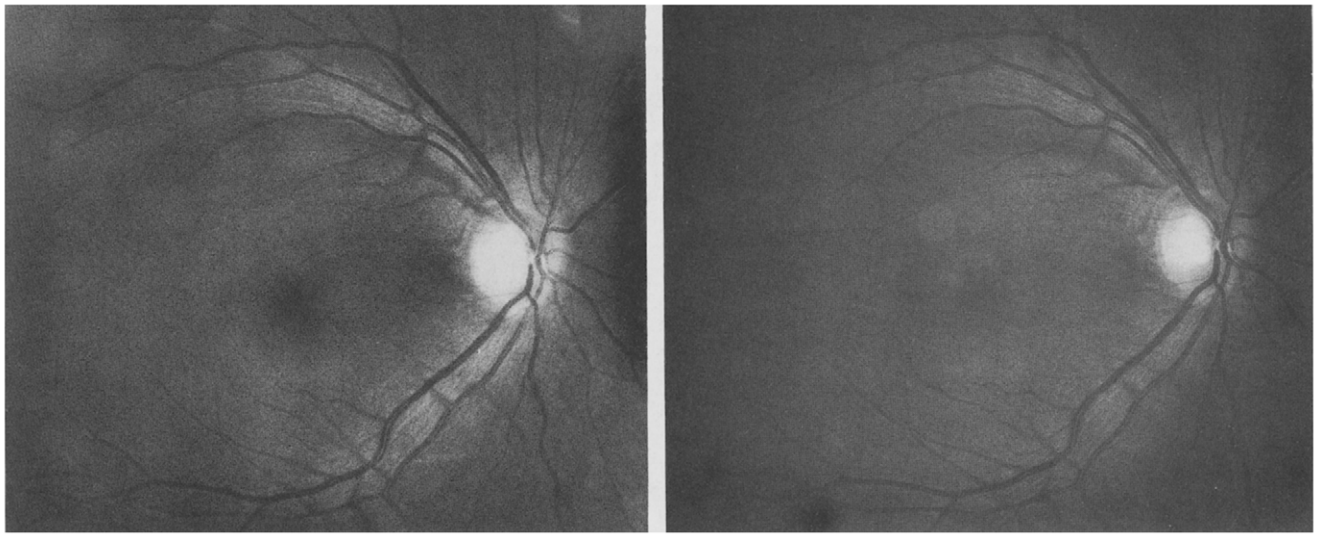


Figure 1. Case 1. A Humphrey 30-2 visual field (July 1991) of the right eye of a 78-year-old woman with intraocular pressure constantly below 20 mmHg (untreated); left eye has advanced low-tension glaucoma. Optic disc stereophotographs showed no change in the optic disc configuration between 1987 and 1992. No visual field defects were found in six Octopus G1 visual fields taken between 1987 and 1990, nor in five Humphrey 30-2 visual fields taken in 1991 (**A, top**). Series of retinal nerve fiber layer photographs from 1987 to 1992 (**B, bottom left,** 1987; **C, bottom right,** 1988. (*Continues*)

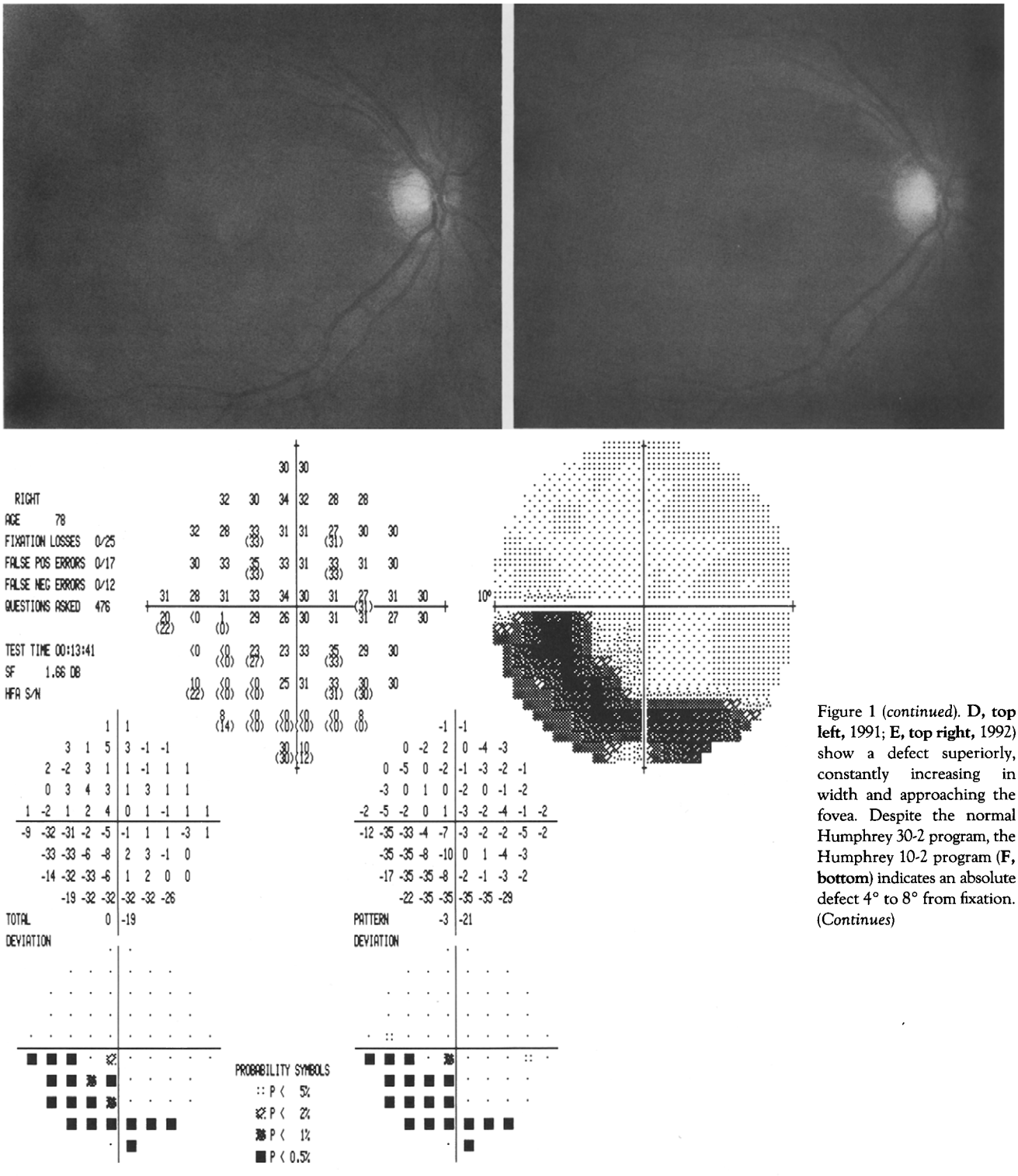
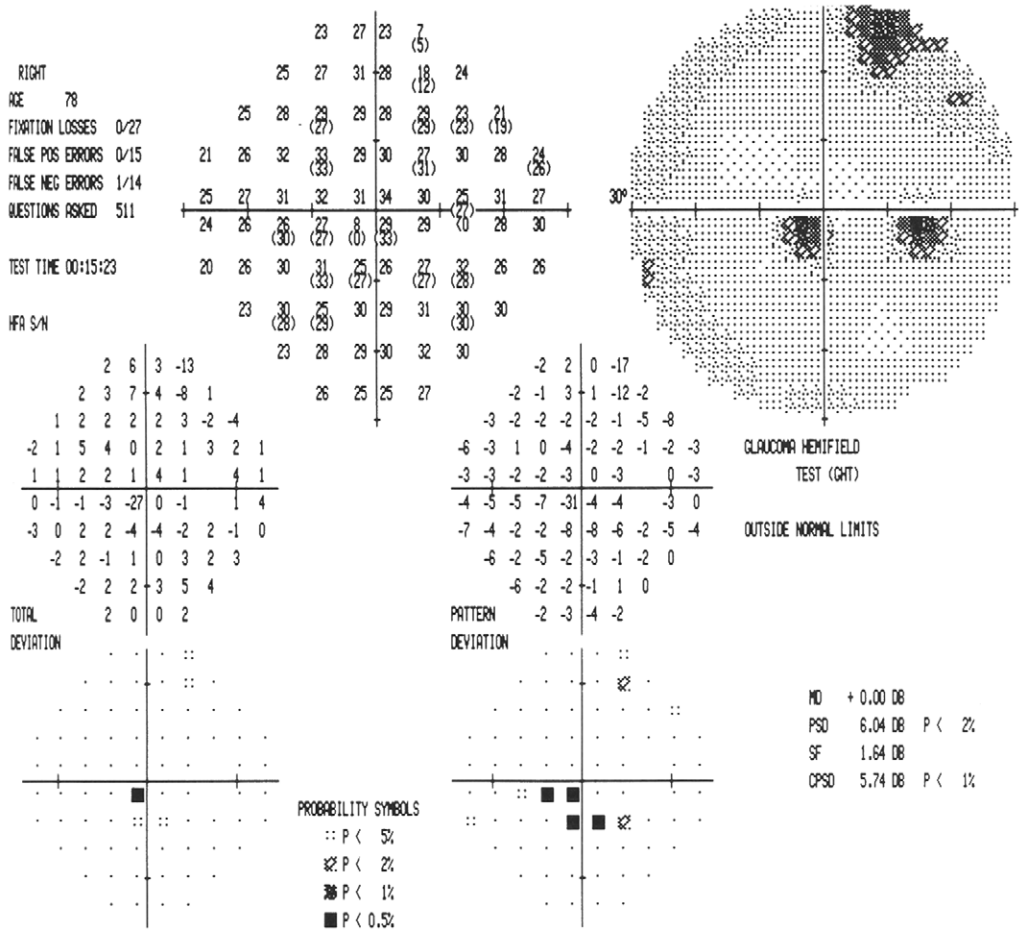


Figure 1 (*continued*). **D, top left,** 1991; **E, top right,** 1992) show a defect superiorly, constantly increasing in width and approaching the fovea. Despite the normal Humphrey 30-2 program, the Humphrey 10-2 program (**F, bottom**) indicates an absolute defect 4° to 8° from fixation. (*Continues*)



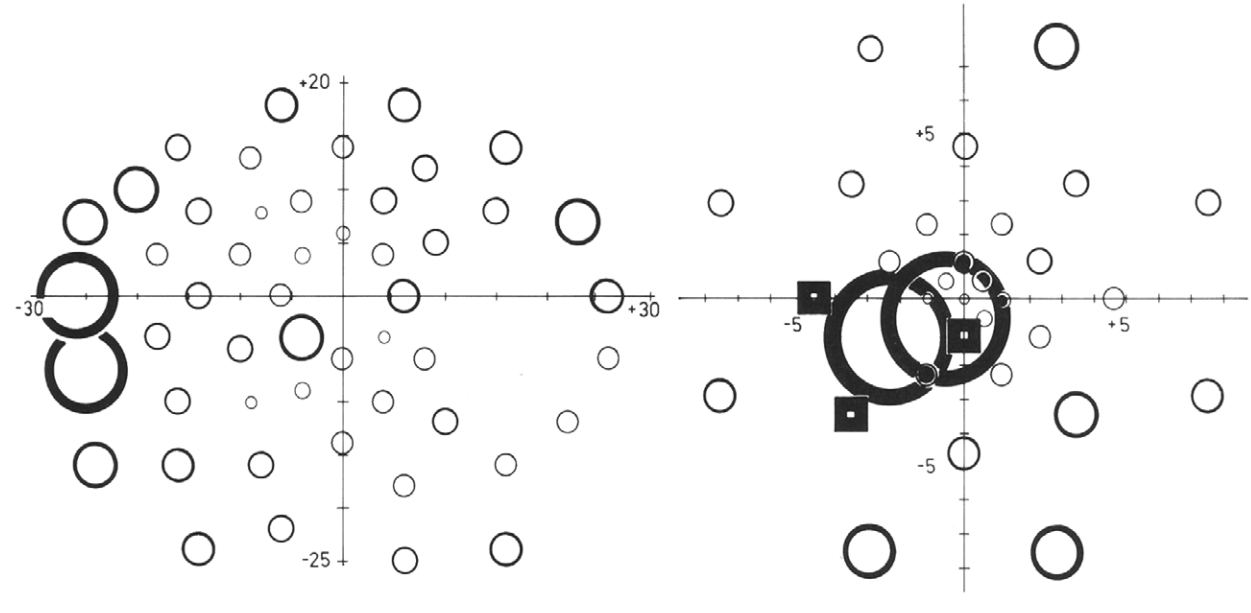


Figure 1 (*continued*). The latest Humphrey 30-2 field taken July 1992 (**G, top**) shows for the first time a localized field defect with threat to fixation. This area was, however, indicated by the pattern deviation plot in **A**. The 30° Ring visual field (**H, bottom left**) shows a nasal step inferiorly. An inferior paracentral scotoma is seen in the Ring (**H**) and Centring (**I, bottom right**) programs.

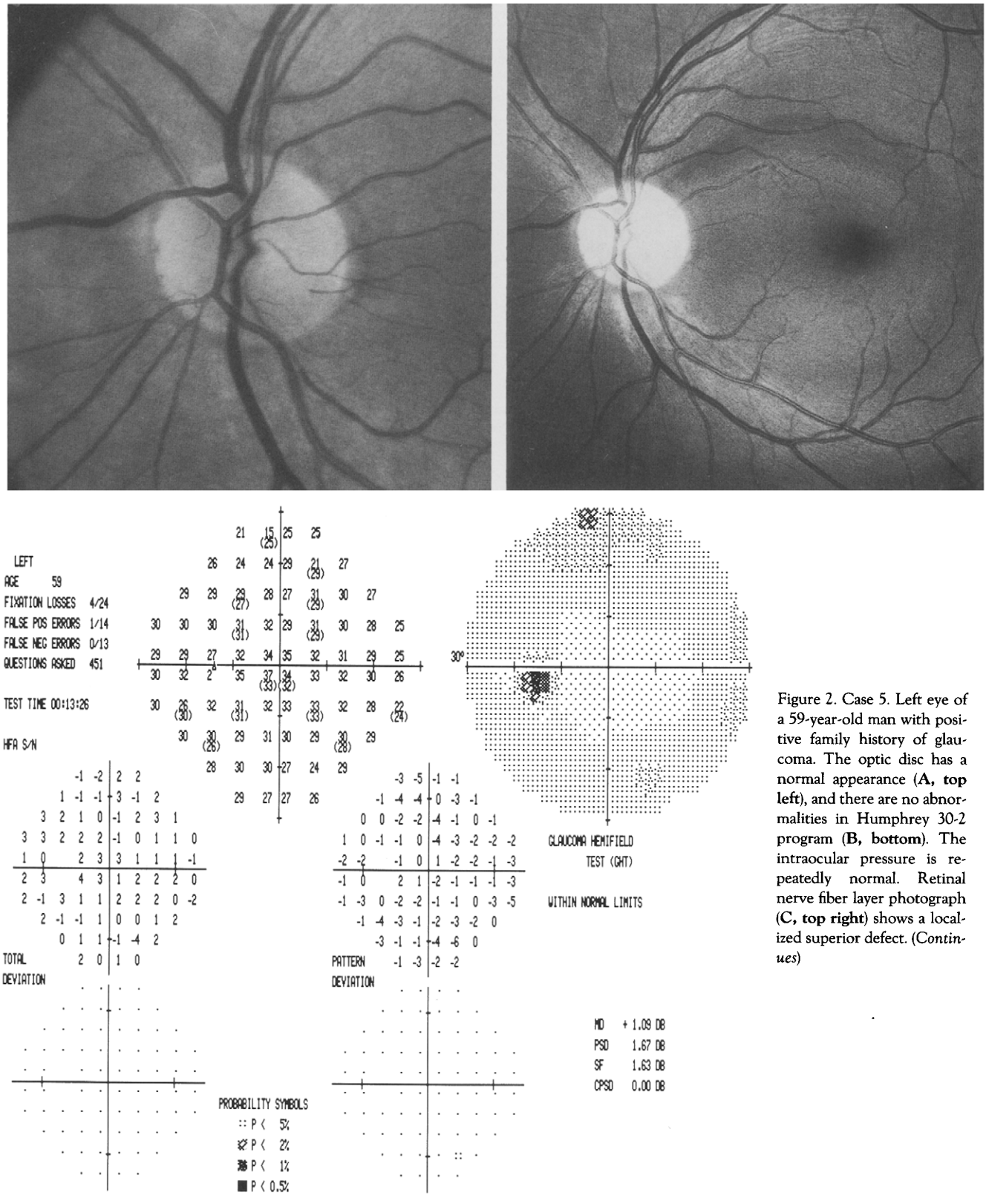


Figure 2. Case 5. Left eye of a 59-year-old man with positive family history of glaucoma. The optic disc has a normal appearance (**A, top left**), and there are no abnormalities in Humphrey 30-2 program (**B, bottom**). The intraocular pressure is repeatedly normal. Retinal nerve fiber layer photograph (**C, top right**) shows a localized superior defect. (*Continues*)

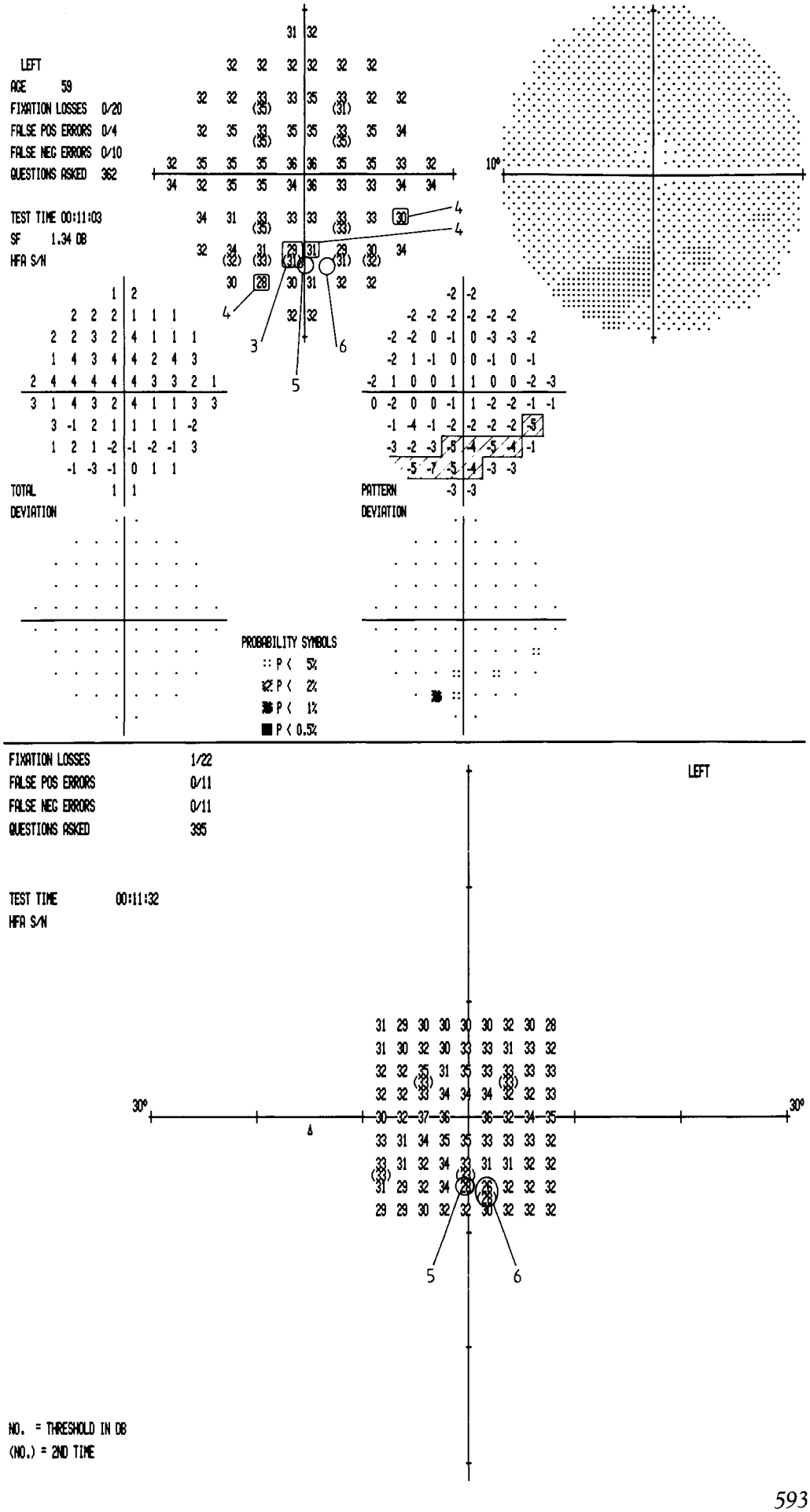
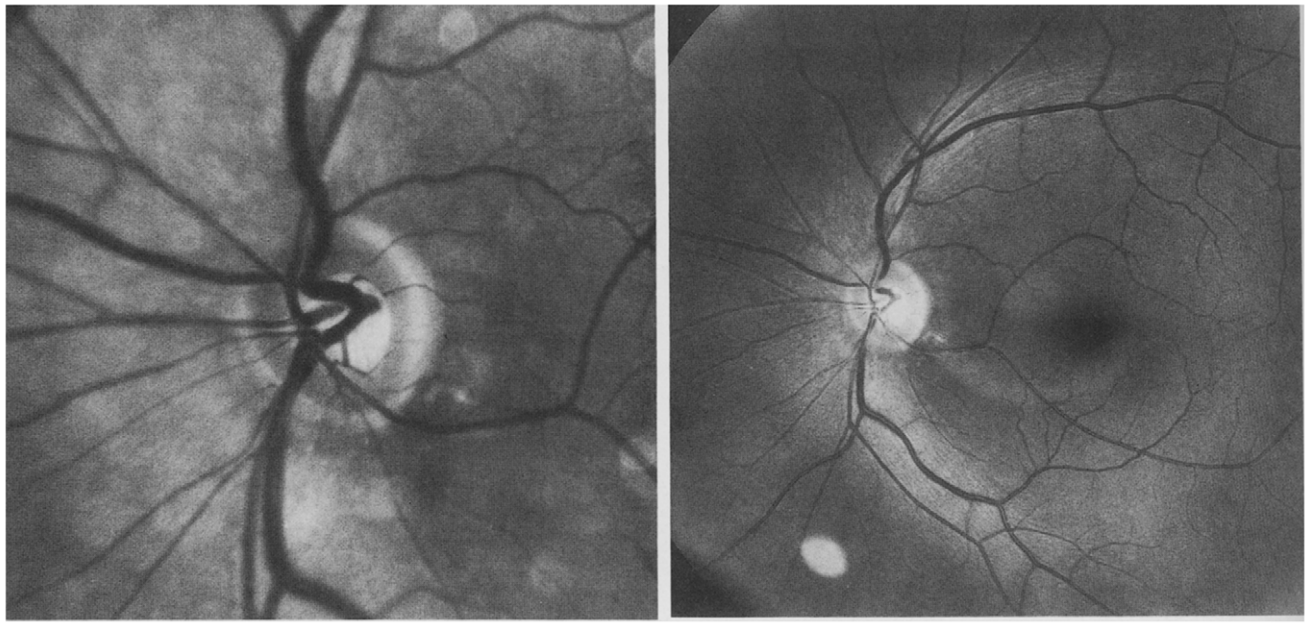


Figure 2 (*continued*). Five to 7° inferiorly from fixation, the threshold values of Humphrey 10-2 (**D, top**) and the on-axis 8° central visual field (**E, bottom**) deviate 3 to 6 decibels from corresponding values in the upper hemifield (squared and circled points, the number indicates the deviation in decibels). This shallow relative field defect, also indicated by pattern deviation plot, corresponds in location to the retinal nerve fiber layer defect.



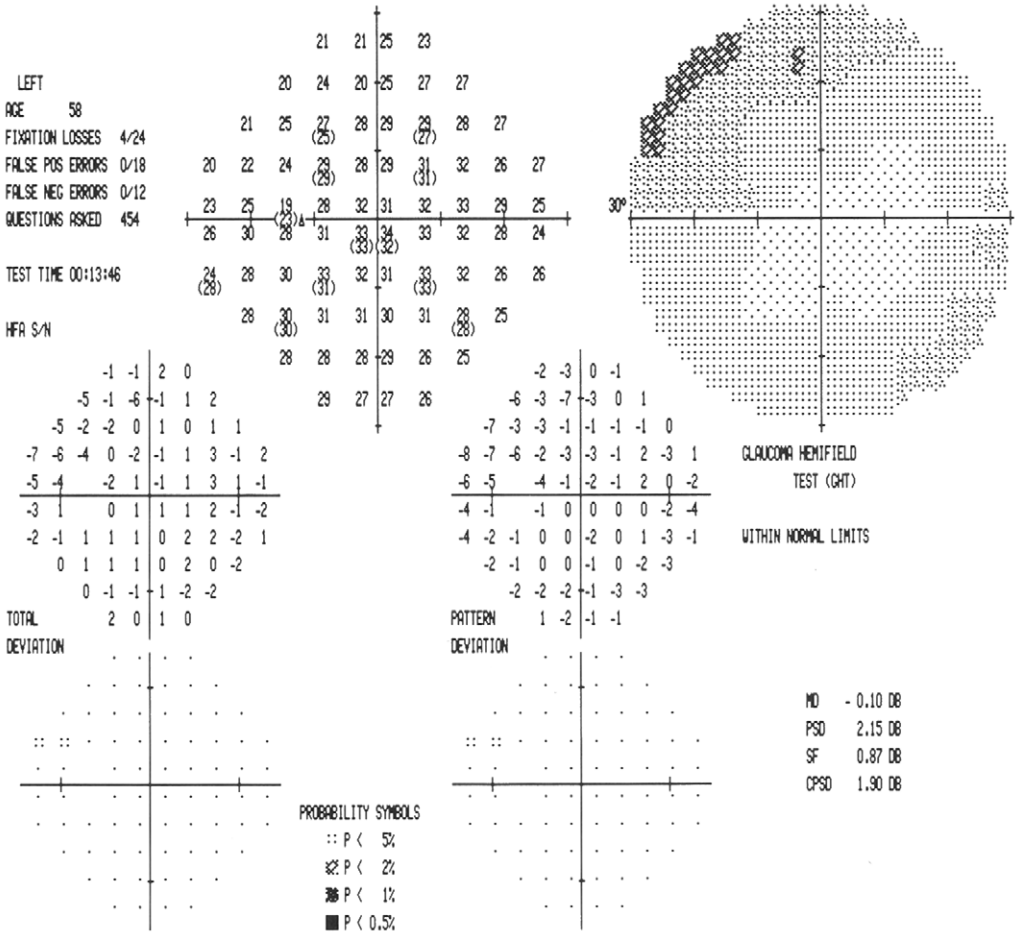
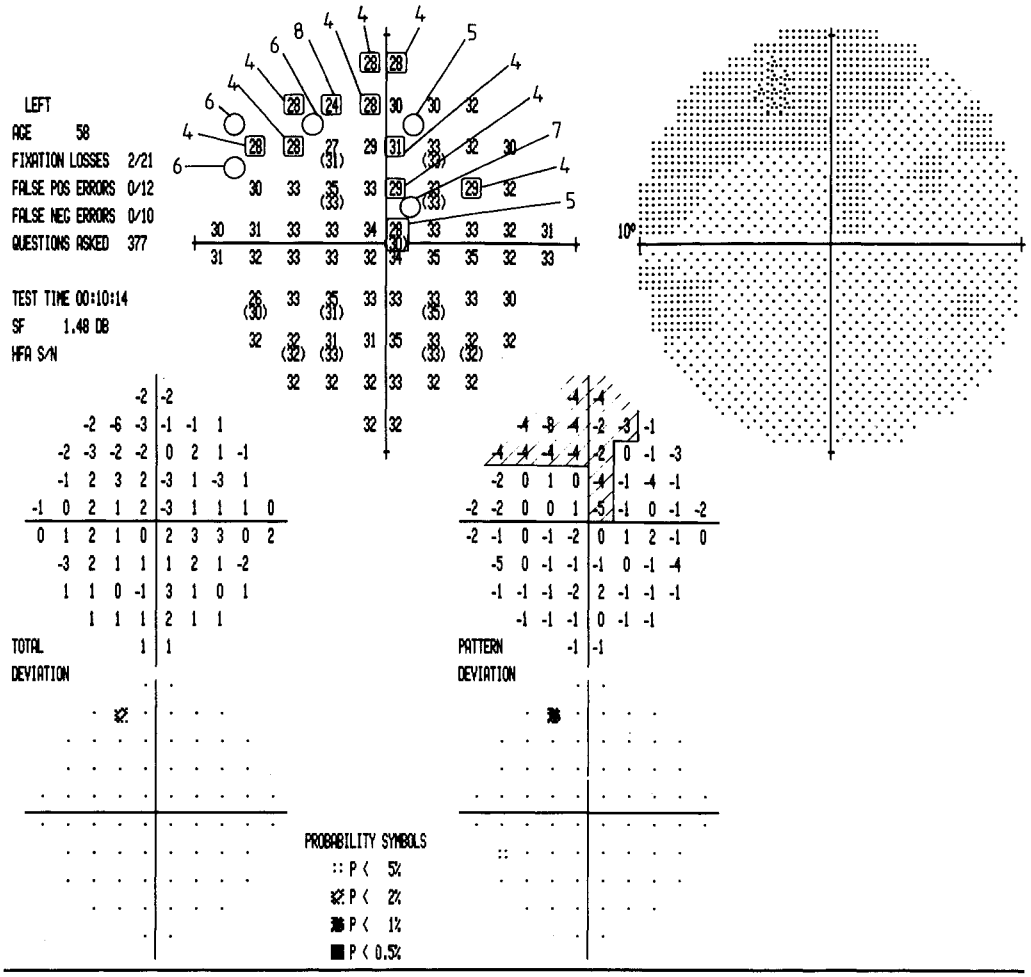


Figure 3. Case 8. Left eye of a 58-year-old man with increased intraocular pressure up to 28 mmHg. The shape of the optic disc cupping follows the shape of the optic disc with abundant neuroretinal rim (**A, top left**). Humphrey 30-2 visual field (**B, bottom**) is normal. There is a broad retinal nerve fiber layer defect inferiorly (**C, top right**). (*Continues*)



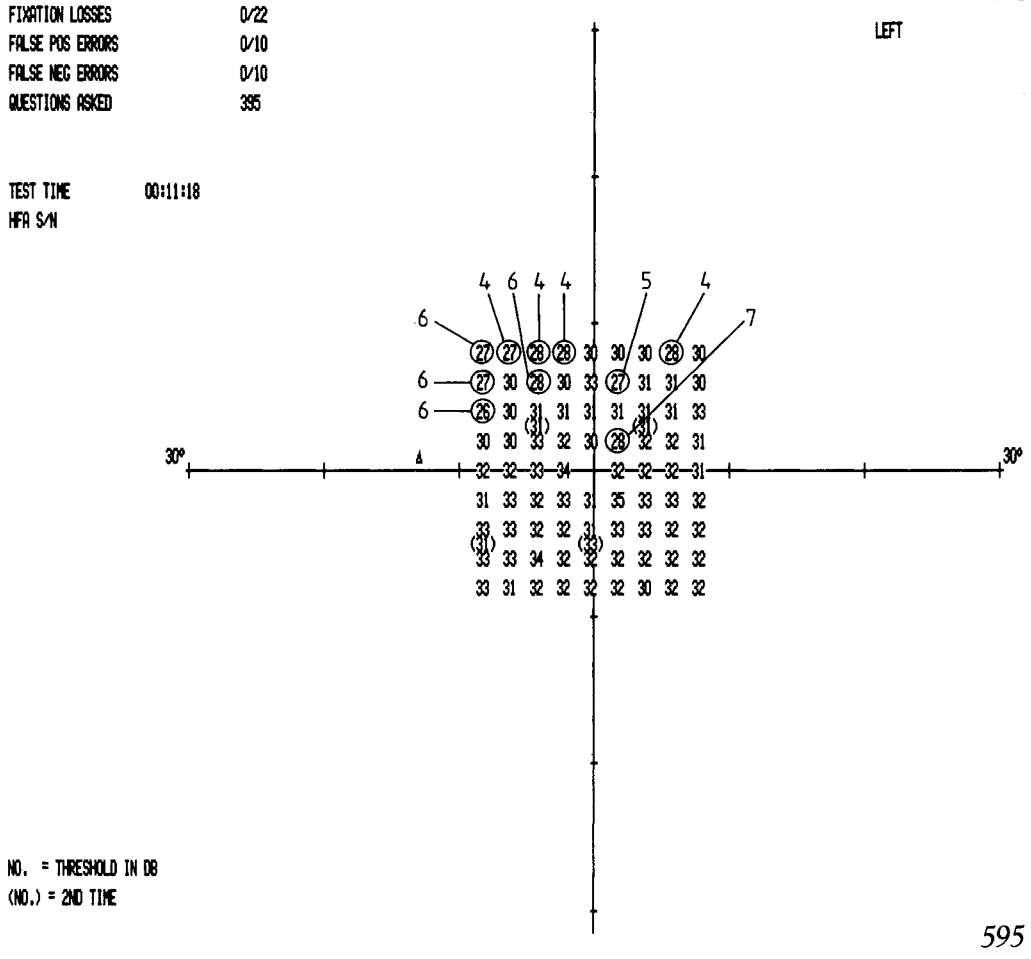


Figure 3 (*continued*). Humphrey 10-2 program (**D, top**) and the on-axis 8° field (**E, bottom**) show a relative defect superiorly (squared and circled points, the number indicates the deviation from corresponding values in the lower hemifield in decibels). This defect is indicated also by the pattern deviation plot. Although the glaucoma hemifield test estimates this field to be normal, there is a difference in the threshold values between upper and lower hemifields also in the Humphrey 30-2 program.

The visual fields also were tested with a high-pass resolution Ophthimus perimeter (HighTech Vision, Malmö, Sweden) using a 30° Ring program and an 8° Centring program. Instead of differential light sensitivity, this test measures the peripheral visual acuity with high-pass spatial frequency ring targets.[9]

In addition to two of us (AT and PJA), the Ring and Centring fields were read by two experts in high-pass resolution perimetry. They were told that some patients may have localized retinal nerve fiber layer defects extending close to fixation. We asked them to indicate whether the Ring and Centring fields were normal or abnormal, and when abnormal, estimate the location of the nerve fiber layer defect. The definition of normality/abnormality included agreement of all four readers in each study eye.

The retinal nerve fiber layer was evaluated from enlarged (18–24 cm) wide-angle black-and-white paper prints (Figs 1–3). The blue (495-nm) filter, built in the Canon wide-angle fundus camera (Canon, Inc, Kawasaki City, Japan), and Panatomic-X film (Eastman Kodak, Rochester, NY) was used. The technique of retinal nerve fiber layer photography has been reported earlier in detail.[13]

Results

A paracentral visual field defect corresponding to the location of the retinal nerve fiber layer defect was found in six of eight patients: in both 10° Humphrey field and Centring programs (2 eyes), in Humphrey only (2 eyes) and in Centring only (2 eyes) (Table 1). In the three cases presented in detail (Figs 1–3), the pattern deviation plot of the Humphrey output was the most sensitive to detect the early visual field loss. In one of the three patients with follow-up, a visual field defect also eventually developed in the Humphrey 30-2 visual field (Fig 1).

The mean test times were the following: Humphrey 30-2, 14.1 ± 2.1 minutes; Humphrey 10-2 program, 11.4 ± 1.2 minutes; user-defined 8° field, 12.6 ± 1.9 minutes; Ring program, 5.2 ± 0.8 minutes; and Centring program, 4.0 ± 0.6 minutes.

Discussion

The results of this study show that normal visual field with normal optic disc appearance does not necessarily indicate absence of glaucomatous abnormality. It seems that the currently used routine threshold programs of automated perimeters are not always optimal or sensitive enough to detect early functional damage in the central area of the visual field. In early stages of glaucoma, estimation of structural abnormalities from serial nerve fiber layer photographs has been reported to be more sensitive than optic disc evaluation.[14]

It was surprising to see how an absolute scotoma could be hidden between the 3° and 9° test points in Humphrey 30-2 program and how sharp the edges of the scotoma are (Fig 1). Combining the 30-2 program with the on-axis 30-1 program would double the test point density, but this has not been recommended for clinical use because repetition of the same test has been considered to be almost as effective as doubling the number of test points.[15]

In clinical work, it is not practical to spend 40 to 50 minutes per eye for visual field examination to find a minute field defect. Such field defects do not hamper the patient's ability to see and require no treatment unless they are progressive. However, the suspicion of glaucoma should lead to follow-up and in case of deterioration, whether structural or functional, initiation of therapy.

More research is needed to develop not only more sensitive but also faster methods for quantitation of functional abnormalities. We have reported earlier a good correlation between semi-quantitative nerve fiber layer score and functional channel fraction-index of the high-pass resolution perimetry.[16] This index is thought to be an expression of functioning retinal ganglion cells and, therefore, also viable nerve fibers in the retina. In the current study, the 5-minute screening program of the high-pass resolution perimeter was as effective as the more time-consuming central Humphrey programs to find functional abnormality in our patients.

In our highly selected material, only two patients had increased IOP. It is not easy to estimate the prevalence of retinal nerve fiber layer abnormalities in eyes with normal optic disc appearance and normal IOP. Such patients may represent a minority but it is important to realize that they do exist and to exclude them from control material in clinical studies. Evaluation of the retinal nerve fiber layer has been criticized for its high false-positive rate of 11% to 17% in normal subjects.[4,17] We may question, however, the normality of these so-called "normal" control eyes. They have been selected using visual field criteria and can therefore be called "field-normal." However, the current study as well the data of more than a thousand patients with ocular hypertension[4,14] show that "field-normality" does not prove normality of the retinal nerve fiber layer and never totally precludes the existence of visual field loss.[18]

The recent experimental methods for quantitation of retinal nerve fiber layer and optic disc abnormalities[19–21] are promising and may help us to evaluate diffuse glaucomatous damage which is the most common[4,22,23] but also the most difficult type of abnormality to detect in the early stages of the disease. It is important to remember that we cannot program an instrument to "see" and measure structures that we do not see ourselves. Even with the help of the most intelligent automated visual field or imaging techniques, it is the ophthalmologist, not the statistician, who makes the diagnosis.

Clinical evaluation of the retinal nerve fiber layer is useful but accurate diagnostics and follow-up currently is not possible without photography.[13,24] Retinal nerve fiber layer evaluation may be difficult and subjective but this also is true for the evaluation of optic discs and statistical outputs of automated visual fields. In agreement with Quigley et al,[14] we believe that every ophthalmologist could and should learn to read retinal nerve fiber layer photographs as an additional diagnostic tool. In addition,

we need to require clinical experience in estimation of retinal nerve fiber layer abnormalities to be able to interpret the quantitative measurements in the future.

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Discussion
by
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Dr. Tuulonen and co-workers presented examples of early glaucoma in which retinal nerve fiber abnormalities (and in one case progression of nerve fiber layer defects) were noticed, the optic disc was normal or nonprogressive, and results of the standard clinical visual field examination did not show a definitive abnormality; but results of a detailed field examination showed a subtle abnormality corresponding to the retinal nerve fiber loss. Thus, there are eyes in which the retinal nerve fiber layer examination provides diagnostic information about mild glaucomatous damage that is undetected by other routine clinical tests.

To use this information in clinical practice, we need to remember that the inverse also is true: there are eyes with a recognizable disc change,[1] abnormal visual fields,[2–4] or both, that do not have recognized retinal nerve fiber abnormalities. There is no answer to the question, "Which occurs first, cupping, retinal nerve fiber layer abnormality, or visual loss?" In fact, as axons are destroyed, there is by necessity simultaneously some minute degree of change in the retinal nerve fiber layer, in the configuration of the optic disc, and in the visual function. Any of the three changes may be the first to reach the threshold of clinical recognition in the earliest stages of the disease, depending on

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variations in the baseline anatomy and physiology of the individual, the manner of examining the retina, disc, and field, and additionally the observer.[3,5] It would be a mistake to conclude that the nerve fiber layer abnormality is invariably the first sign of damage to appear, and that therefore a visual field examination is unnecessary if the nerve fiber layer appears normal in a person being tested for glaucoma because of an abnormal intraocular pressure (IOP) or a suspicious excavation of the disc. The same is true in evaluating progression: progressive changes in the nerve fiber layer often reflect a change in the field, but field progression can often occur without visual change in the nerve fiber layer.[6]

A second point of clinical relevance is that the specificity of finding a retinal nerve fiber layer abnormality is imperfect: retinal nerve fiber layer abnormality occurs with nonglaucomatous disease that affects the inner retina or optic nerve[7,8] and the abnormality may be mimicked in normal individuals.[2–4] Therefore, interpretation of an abnormal retinal nerve fiber layer appearance depends on the clinical setting, for example on evidence of nonglaucomatous disease, and in a glaucoma suspect on the presence of corroborating evidence of IOP-induced damage. In a glaucoma suspect who on initial evaluation has a retina with a nerve fiber layer abnormality as the only sign of damage, it makes sense to undertake more frequent or more detailed examinations, as done by these authors, to determine if the patient truly has the beginning of progressive glaucoma. If an abnormal appearance of the retinal nerve fiber is the only finding, it may take time to determine if it is a false-positive or a true-positive finding that will progress into more manifest damage. If it is a true finding, the apparent retinal abnormality likely represents early, slowly progressive glaucoma. In such early cases, it is permitted to delay treatment not only to document that it is a true abnormality, but also to gauge how rapidly progressive the case is and how seriously the ultimate visual function is threatened. The need for immediate effective therapy is not as great as for the patient with major nerve fiber loss, cupping, and fully manifest visual disfunction, which represents a more serious threat of visual disability if the IOP is unchecked.

In summary, a careful nerve fiber layer examination can help find early damage that otherwise may be missed, and is a worthy addition to our diagnostic endeavors. However, it should supplement rather than replace other diagnostic tests, and it would be a mistake to omit visual field examination in the diagnosis or follow-up of patients, just because results of the nerve fiber layer examination were normal or unchanging. Moreover, in the event that a nerve fiber layer defect is the only suggestion of glaucoma, it would be appropriate to look more diligently for a confirmatory evidence of damage or wait for evidence of progression before embarking on aggressive therapy to lower the IOP.

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